

## PROTOCOL

**STUDY TITLE:** *Safety and Efficacy of Intravitreal Ranibizumab for Diabetic Macular Edema Previously Treated with Intravitreal Bevacizumab: A Randomized Dual-Arm Comparative Dosing Trial (Phase:1/2): REACT Study*

**STUDY DRUG** Recombinant humanized anti-VEGF monoclonal antibody fragment (rhuFab V2 [ranibizumab])

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## TABLE OF CONTENTS

	<u>Page:</u>
1. BACKGROUND .....	1-6
1.1 Pathophysiology .....	1
1.2 Treatment.....	1-2
1.3 Ranibizumab .....	2-3
1.4 Nonclinical Experience with Ranibizumab.....	3-6
1.4.1 Nonclinical Pharmacokinetics .....	3
1.4.2 Nonclinical Toxicology .....	4
1.4.3 Stability Studies .....	4
1.5 Clinical Experience with Ranibizumab.....	4-6
2. OBJECTIVES.....	6-7
2.1 Primary Objective .....	7
2.2 Secondary Objective .....	7
3. STUDY DESIGN .....	8-10
3.1 Description of the Study .....	8
3.2 Rationale for Study Design.....	8-9
3.3 Outcome Measures .....	9
3.3.1 Primary Outcome Measures .....	9
3.3.2 Secondary Outcome Measures .....	9
3.4 Safety Plan.....	9-10
3.5 Compliance with Laws and Regulations.....	10
4. MATERIALS AND METHODS .....	10-21
4.1 Subjects .....	10-12
.....	
4.1.1 Subject Selection .....	10-11

## TABLE OF CONTENTS (cont'd)

	<b><u>Page</u></b>
4. MATERIALS AND METHODS (cont'd)	
4.1.2 Inclusion Criteria .....	11
4.1.3 Exclusion Criteria .....	11-12
4.2 Method of Treatment Assignment .....	12
4.3 Study Treatment.....	13-15
4.3.1 Formulation.....	13
4.3.2 Dosage, Administration, and Storage .....	13-15
4.4 Concomitant and Excluded Therapies.....	15
4.5 Study Assessments.....	15-19
4.5.1 Assessments during the Treatment Period .....	15-19
4.5.2 Early Termination Assessments.....	19
4.6 Subject Discontinuation.....	19-20
4.7 Study Discontinuation.....	20
4.8 Statistical Methods .....	20-21
4.8.1 Analysis of the Conduct of the Study.....	20
4.8.2 Safety Analyses .....	20
4.8.3 Efficacy Analyses.....	21
4.8.4 Missing Data .....	21
4.8.5 Interim Analyses .....	21
4.9 Data Quality Assurance .....	21
5. ASSESSMENT OF SAFETY.....	22-32
5.1 Adverse Events .....	22
5.2 Serious Adverse Events .....	23
5.3 Methods and Timing for Assessing and Recording Safety Variables	23-24
5.4 Evaluations.....	24-25
5.5 Vital Signs .....	25
5.6 Procedures for Eliciting, Recording, and Reporting Adverse Events.	25-32

TABLE OF CONTENTS (cont'd)

	<b><u>Page</u></b>
5.6.1 Eliciting Adverse Events .....	25
5.6.2 Specific Instructions for Recording Adverse Events.....	25-28
5.6.3 Med Watch 3500A Reporting Guidelines .....	28
5.6.4 Follow-up Information .....	28-29
5.6.5 Additional Reporting Requirements for IND Holders.....	29-31
5.6.6 Safety Reporting Fax Cover Sheet .....	32
<b>6 INVESTIGATOR REQUIREMENTS.....</b>	<b>33-37</b>
6.1 Study Initiation.....	33
6.2 Study Completion .....	33-34
6.3 Informed Consent Form .....	34-35
6.4 Institutional Review Board or Ethics Committee Approval.....	35-36
6.5 Case Report Forms .....	36
6.6 Study Drug Accountability.....	36
6.7 Disclosure of Data .....	36
6.8 Retention of Records.....	37
6.9 Study Close-Out.....	37
<b>REFERENCES .....</b>	<b>38-39</b>
 <b>APPENDICES</b>	
Appendix A: Study Flowchart.....	40-42
Appendix B: Pre-Injection Procedures for All Subjects.....	43
Appendix C: Analysis of Similar Events .....	44-45

## **1. BACKGROUND**

### **1.1 PATHOPHYSIOLOGY**

Diabetic macular edema (DME) is the most common cause of vision loss from diabetic retinopathy. It is characterized by macular swelling secondary to increased vascular permeability secondary to loss of pericytes in the macular vascular bed. Clinically, microaneurysms and exudates are often seen in association with macular edema. Foveal-involving cystic changes and macular edema can have significant impact on visual loss. Extent of perfusion and ischemia also is important for visual prognosis.

Multiple factors play a role in the evolution of diabetic macular edema. Vascular endothelial growth factor has been shown to be significantly elevated in diabetic retinopathy and may play an important role in the evolution and pathogenesis of DME. Increasing VEGF levels are also seen in the setting of progressive ischemia, such as proliferative diabetic retinopathy when extensive peripheral nonperfusion may be present.<sup>1</sup> Reducing the active levels of VEGF may have significant positive consequences for outcomes related to DME management.

### **1.2 TREATMENT OF DIABETIC MACULAR EDEMA**

Following the Early Treatment of Diabetic Retinopathy Study (ETDRS), focal/grid laser photocoagulation became the standard treatment for DME. This therapy may continue to have an important place in the treatment of macular edema. Utilizing laser photocoagulation, the ETDRS achieved stabilized vision for a significant number of patients with diabetic macular edema.<sup>2</sup>

However, advances in pharmacotherapy have resulted in exciting new treatment modalities for DME. The Diabetic Retinopathy Clinical Research Network (DRCR.net) conducted a study comparing intravitreal triamcinolone to laser photocoagulation. In this study laser photocoagulation performed better over the long-term with reduced side effects.<sup>3</sup> However, other studies have suggested that particularly in pseudophakic patients, steroids are an important treatment alternative.<sup>4</sup> Long-lasting steroid delivery systems are also currently under investigation, including a dexamethasone implant and fluocinolone implant. Results from these studies are promising but at this time these

devices are still under investigation and are not FDA-approved in the United States.<sup>5, 6</sup>

Since the initial publication of the DRCR.net study that suggested superiority of ranibizumab to laser photocoagulation, VEGF inhibitors have become a first-line therapy for DME.<sup>4</sup> Bevacizumab which is not approved for ophthalmic indications is among the most frequently used anti-VEGF agents. The BOLT study was a 2-year randomized controlled trial comparing bevacizumab to laser photocoagulation. Bevacizumab was given with a loading dose every 6 weeks for three injections and then retreatment occurred every 6 weeks. Bevacizumab performed significantly better than the laser group with a median gain of 9 letters compared to 2.5 letters. Nearly 50% of eyes gained 2 lines or more compared to 7% of the laser group.<sup>7, 8</sup> Given the limited size of the bevacizumab studies, conclusions regarding safety remain difficult.

Aflibercept is also being studied in the treatment of DME. In comparison to laser photocoagulation, the various dosing regimens of aflibercept showed a 9.7-12.0 letter gain compared to -1.3 letters for the laser group. When examining eyes with 3 line gain or more, 23.8-45.5% of eyes treated with aflibercept compared to 11.4% for the laser group.<sup>9</sup> Aflibercept remains investigational at this time for the treatment of DME.

Ranibizumab is the first and currently only VEGF inhibitor approved for the treatment of DME. The results of the RISE/RIDE trials showed that 33.6 to 44.8% of eyes gained more than 3 lines at 2 years compared to 12.3-18.3% of sham eyes. Laser photocoagulation was allowed as a rescue therapy. Based on the results of the RISE/RIDE trials, the FDA approved ranibizumab 0.3 mg for the treatment of DME in August 2012.<sup>10</sup>

### **1.3 RANIBIZUMAB AND DIABETIC MACULAR EDEMA**

As noted above, the pivotal RISE/RIDE phase III trials resulted in the FDA approval of ranibizumab for the treatment of DME. Numerous trials have suggested the efficacy and safety of ranibizumab in the treatment of DME, including the DRCR.net, READ, and RISE/RIDE.<sup>4, 10, 11</sup> The results of these studies suggest that intravitreal ranibizumab therapy is a safe and effective

treatment modality for DME. Ranibizumab therapy results in functional stabilization in the vast majority of eyes and in significant improvement in nearly half of eyes. Additionally, RISE/RIDE revealed that eyes treated with ranibizumab had lower rates of retinopathy progression and higher rates of retinopathy improvement. In addition to the functional improvements, ranibizumab resulted in significant anatomic improvements with a mean reduction of ~ 250 microns in central foveal thickness compared to only 133 micron decrease in the laser group.<sup>10</sup>

Prior to the approval of ranibizumab, bevacizumab was the only readily available VEGF inhibitor being utilized (off-label) for the treatment of DME. Although the functional results to bevacizumab therapy, appear promising, the systemic safety of bevacizumab for DME and the relative efficacy of bevacizumab compared to ranibizumab remain unknown. With ranibizumab's approval, it is unclear whether switching from bevacizumab to ranibizumab has a clinical impact on the disease course. Given the number of eyes treated with bevacizumab, answering this question is important. These questions are the focus of this investigation.

## **1.4 NONCLINICAL EXPERIENCE WITH RANIBIZUMAB**

### **1.4.1 Nonclinical Pharmacokinetics**

The pharmacokinetics of ranibizumab have been investigated in rabbits and cynomolgus monkeys following intravitreal and intravenous administration. In both species, following intravitreal administration, ranibizumab was cleared from the vitreous humor with a half-life of 2–3 days. Following single intravitreal administration to cynomolgus monkeys, retinal concentrations of ranibizumab were approximately one-third of vitreous concentrations and declined in parallel with vitreous concentrations. In humans, the intravitreal half-life of ranibizumab is estimated to be 9 days. Repeated intravitreal injections of ranibizumab can lead to detectable antibodies in serum in rabbits and cynomolgus monkeys.

#### **1.4.2 Nonclinical Toxicology**

A series of nonclinical studies of ranibizumab administered by intravitreal injection to cynomolgus monkeys have been performed (details regarding study design and results can be found in the Investigator Brochure).

#### **1.4.3 Nonclinical Data Supporting the Anti-Edema Activity of Ranibizumab**

In Studies 01-401E-1757 and 01-401G-1757, the effect of ranibizumab on vascular leakage was explored using a modified Miles assay in the guinea pig. Ranibizumab demonstrated a concentration-dependent effect of blunting the vascular permeability induced by VEGF. These results are consistent with the decrease in retinal vascular permeability as observed on optical coherence tomography (OCT) and fluorescein angiography in AMD and diabetic macular edema studies and further support the rationale for the use of ranibizumab in CRVO and BRVO, in which vascular permeability plays a significant role in the pathology

### **1.5 CLINICAL EXPERIENCE WITH RANIBIZUMAB**

Ranibizumab has been or is being studied in more than 5000 subjects with neovascular AMD, retinal vascular occlusive disease, and diabetic retinopathy/macular edema in a number of Phase I, I/II, II, III, and IIIb clinical trials. Ranibizumab is contraindicated in patients with ocular or periocular infections and in those with known hypersensitivity to ranibizumab or any of the excipients in ranibizumab. Intravitreal injections, including those with ranibizumab, have been associated with endophthalmitis and retinal detachment. Proper aseptic injection technique should always be used when administering ranibizumab. Increases in IOP have been noted within 60 minutes of intravitreal injection with ranibizumab. Therefore, IOP as well as perfusion of the optic nerve head should be monitored and managed appropriately. Serious adverse events related to the injection procedure have occurred in <0.1% of intravitreal injections include endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract. Other serious ocular adverse events observed among ranibizumab-treated subjects and occurring in <2% of subjects included intraocular inflammation and increased IOP. The most common adverse reactions (reported  $\geq 6\%$  higher in ranibizumab-treated subjects

than control subjects) were conjunctival hemorrhage, eye pain, vitreous floaters, increased IOP, and intraocular inflammation.

Although there was a low rate (<4%) of arterial thromboembolic events (ATEs) observed in the ranibizumab clinical trials there is a potential risk of ATEs following intravitreal use of inhibitors of VEGF. The rate of ATEs in three studies (FVF2598g, FVF2587g, and FVF3192g) in the first year was 1.9% of subjects in the combined group of subjects treated with 0.3 mg or 0.5 mg ranibizumab compared with 1.1% of subjects in the control arms of the studies. In the second year of Study FVF2598g and FVF2587g, the rate of ATEs was 2.6% of subjects in the combined group of those treated with 0.3 mg or 0.5 mg ranibizumab compared with 2.9% of subjects in the control arm. The most common non-ocular adverse reactions observed in  $\geq 15\%$  of ranibizumab-treated subjects that occurred more frequently than in control subjects included, nasopharyngitis, headache, and upper respiratory tract infection.

The Sailor study (FVF3689g) evaluated the safety of intravitreal ranibizumab in a large population of subjects with CNV secondary to AMD. Subjects in Cohort 1 (N=2378) were randomized (1:1) to receive ranibizumab at a dose level of 0.3 mg or 0.5 mg; subjects were masked to these dose levels. Treatment was administered monthly for three initial doses (Day 0, Month 1, and Month 2), with scheduled follow-up visits on Months 3,6,9, and 12. Retreatment after the first three injections was performed as needed, on the basis of predefined criteria with injections no more frequently than every 30 days.

Cohort 2 (N=1992) consisted of subjects enrolled after the majority of Cohort 1 subjects had been enrolled, with enrollment continuing until ranibizumab was approved or denied by the FDA for US marketing, and if approved, until commercially available or 30 September 2006, whichever was earlier. Subjects in Cohort 2 received open-label ranibizumab at the 0.5 mg dose level, with an initial injection on Day 0 followed by retreatment at the physician's discretion, no more frequently than every 30 days. Subjects were monitored for safety for a total of 12 months; safety information, including both serious and nonserious adverse events, was collected at every clinic visit, with two formal safety visits scheduled at Months 6 and 12.

The study consisted of a 30-day screening period and a 1-year treatment period. Treatment duration was approximately 197 days for both dose groups in Cohort 1 and 144 days for subjects in Cohort 2. The mean follow-up time differed between Cohort 1 and Cohort 2, 337 days versus 254 days, respectively.

Ranibizumab was well tolerated, and the incidence of ocular SAEs and AEs was low and unrelated to dose. The rates of individual key ocular SAEs in Cohort 1 were < 1% and were similar across dose groups. Endophthalmitis or presumed endophthalmitis developed in 0.2% subjects in the 0.3-mg group and 0.4% subjects in the 0.5-mg group. The incidence of ocular inflammation, including iritis, uveitis, vitritis, and iridocyclitis was 1.9% in the 0.3-mg group and 1.5% in the 0.5-mg group. Overall cataract rates were 5.4% (0.3 mg) and 6.0% (0.5 mg) and were similar when broken down by nuclear, subcapsular, and cortical subtypes. The rates of individual key ocular SAEs in Cohort 2 were <1%.

The rates of key non-ocular SAEs and AEs, including Antiplatelet Trialists' Collaboration (APTIC) ATEs, MI, and vascular death were similar for cohorts 1 and 2 and 0.3- and 0.5-mg dose groups. The incidence of MI and non-ocular hemorrhage was similar across Cohort 1 dose groups. APTIC ATEs, including vascular and unknown deaths, nonfatal MI, and nonfatal cardiovascular accidents, were similar across dose groups. During the 12-month study period, 0.7% of subjects in the 0.3-mg group and 1.2% of subjects in the 0.5-mg group suffered a stroke. The number of vascular deaths and deaths due to unknown cause did not differ across dose groups. Rates of key non-ocular SAEs in Cohort 2 were generally lower than those in Cohort 1.

Refer to the Ranibizumab Investigator Brochure or Lucentis® Package Insert for additional details regarding clinical safety experience with ranibizumab.

## **2. OBJECTIVES**

The utility and efficacy of ranibizumab in eyes with DME that are naïve to VEGF inhibitors has been shown in the RISE/RIDE trials and others.

<sup>4,10,11</sup>However, many eyes have been previously treated (recent and frequent)

with other VEGF inhibitors (in particular, bevacizumab). Our primary objective is to understand the functional and anatomic effectiveness of ranibizumab following previous anti-VEGF. Additionally, the optimal dosing regimen remains to be determined. Monthly dosing was evaluated in the RISE/RIDE trials, but monthly dosing may not be necessary or practical in all patients. This study will also compare a “treat-and-extend” dosing regimen to a monthly dosing regimen.

## **2.1 Primary Objective**

The primary objective of the study is to assess the ocular and systemic adverse events of ranibizumab for DME following previous treatment with intravitreal bevacizumab (worsened acuity >30 letters, retinal detachment, endophthalmitis, cataract progression, vitreous hemorrhage, new PDR or neovascularization of the iris or angle, systemic thromboembolic events, deaths and systemic serious adverse events).

## **2.2 Secondary Objectives**

The secondary objectives include:

- mean change from baseline in best-corrected visual acuity at months 6 and 12
- mean absolute change from baseline central foveal thickness at months 6 and 12 as measured by SDOCT (defined as the average thickness within the central 1 mm subfield)
- proportion of subjects that were anatomically “dry” by SDOCT at months 6 and 12
- proportion of participants who gained greater than or equal to 15 letters of vision at months 6 and 12
- proportion of participants who lost greater than or equal to 15 letters of vision at months 6 and 12
- proportion of patients that are 20/40 or better at months 6 and 12
- comparison of extent of angiography leakage from baseline to months 3, 6, and 12,
- comparison of peripheral nonperfusion from baseline to months 3, 6 and 12
- total number of injections

- Assessment of pre-trial anatomic improvement based on OCT on bevacizumab prior to switching to ranibizumab. Analysis will also be stratified based on subsequent response to ranibizumab.
- Assessment of pre-trial functional improvement based on snellen visual acuity prior to switching to ranibizumab. Analysis will also be stratified based on subsequent response to ranibizumab.

### 3. **STUDY DESIGN**

#### 3.1 **DESCRIPTION OF THE STUDY**

This is an open-label, Phase I/II study of intravitreally administered 0.3mg ranibizumab in subjects with DME previously treated with intravitreal bevacizumab with a randomized comparative dosing strategy (monthly vs “treat-and-extend”). Thirty patients total will be enrolled in the study, 15 in each group. This study will have a 1-year treatment period. The recruitment period will occur over 1 year with a total potential study duration of 2 years. Interim analysis performed at 6 months and final analysis at 1 year.

Group 1 (monthly group) n=15

- Consented, enrolled subjects will receive multiple open-label intravitreal injections of 0.3 mg ranibizumab administered every **30 days** (+/- 7 days from the last treatment) for **12** months in the monthly group.

Group 2 (“treat-and-extend” group) n=15

- In the “treat-and-extend” group, eyes will be treated with 3 loading doses at 30-day intervals (+/- 7 days from the last treatment). After the third loading dose, the follow-up interval is determined with an OCT-based protocol.

Angiography assessment:

Both qualitative and quantitative assessment of angiographic features will be performed on obtained angiograms. This will include evaluation of leakage, microaneurysms and ischemia. This is detailed in Appendix D. Addendum for

Prior anti-VEGF response assessment:

Utilizing available clinical and imaging data contained in the medical record, assessment of functional (visual acuity) and anatomic (OCT) responses will be assessed. This information would be assessed in detail following review of this data for appropriate inclusion/exclusion parameters for the study. This is detailed in Appendix E.

### **3.2 RATIONALE FOR STUDY DESIGN**

RISE/RIDE have shown that ranibizumab is an effective treatment for DME in anti-VEGF naïve eyes. However, many patients have been previously treated with bevacizumab or are initially started on bevacizumab. The efficacy and safety of ranibizumab following previous bevacizumab therapy is unknown. In addition to better understanding the role for ranibizumab following bevacizumab, this study also aims to evaluate a dosing regimen that reduces treatment/visit burden. Diabetes is a chronic disease and often these patients are younger than the age-related macular degeneration population. The burden of monthly visits and cumulative risk of monthly treatment over years should not be ignored and is likely not practical. This study will evaluate one of the most popular anti-VEGF treatment regimens for neovascular age-related macular degeneration: “treat-and-extend.” This novel approach minimizes visits and treatment while maximizing the anatomic results [minimizing the cycle of edema recurrence that triggers therapy in a pro re nata (PRN) regimen].

#### **Addendum for Quantitative Assessment of Ultra-Widefield Angiographic Features in Diabetic Macular Edema**

Objective and quantitative assessment of angiographic imaging is currently lacking. Subjective interpretation of angiographic patterns and features limit the analysis and potential of utilizing the modality as a true biomarker of diagnostic and therapeutic value. The complex patterns noted within angiography, including staining, leakage, pooling, blockage, nonperfusion, and window defects are amenable to quantitative assessment and integrative analysis for pattern recognition. This complex pattern analysis could be utilized to create an activity fingerprint that may have value in therapeutic assessment and monitoring.

Common angiographic features in DME in these conditions include vascular staining/leakage, microaneurysms, capillary nonperfusion, and neovascularization. Differential response to anti-VEGF therapy is quite

frequent among patients, vascular patterns and angiographic features may provide important insight into the optimal therapeutic or reason for lack of response. The ability to objectively characterize the patterns and features of the angiographic features would be an important advance in characterizing retinal vascular conditions.

### **3.3 OUTCOME MEASURES**

#### **3.3.1 Primary Outcome Measures**

The primary outcome measures for safety and tolerability are the following:

- Incidence and severity of ocular adverse events, as identified by eye examination (including visual acuity testing)
- Incidence and severity of other non-ocular adverse events, as identified by physical examination, subject reporting, and changes in vital signs

#### **3.3.2 Secondary Outcome Measures**

- Mean change in best-corrected visual acuity as assessed by the number of letters read correctly on the electronic ETDRS eye chart from baseline to months 6 and 12.
- Mean absolute change from baseline central foveal thickness at months 6 and 12 as measured by SDOCT (defined as the average thickness within the central 1 mm subfield)
- Proportion of eyes that were anatomically “dry” by SDOCT at months 6 and 12.
- Proportion of eyes gaining greater than or equal to 15 letters of vision at months 6 and 12.
- Proportion of eyes losing greater than or equal to 15 letters of vision at months 6 and 12.
- Proportion eyes with 20/40 or better best-corrected visual acuity at months 6 and 12.
- Comparison of extent of angiographic leakage from baseline to months 3, 6 and 12.
- Comparison of extent of peripheral nonperfusion from baseline to months 3, 6, and 12.
- Comparison of previous anatomic anti-VEGF response to month 3, month 6, and month 12 anatomic response.

- Comparison of previous functional anti-VEGF response to month 3, month 6 and month 12 functional response

### **3.4 SAFETY PLAN**

The safety assessments to be conducted for this study are listed in Section 4.5 and Appendix A.

Potential ocular adverse events associated with intravitreal injections include ocular irritation, subconjunctival hemorrhage, corneal abrasion, floaters, vitreous hemorrhage, retinal tear, retinal detachment, endophthalmitis, lens damage, and intraocular inflammation. The risk of severe ocular side effects (e.g., endophthalmitis, retinal detachment) is approximately 1/1000. Potential theoretical systemic adverse events include stroke and myocardial infarction. However, patients with diabetes are also at higher risk of stroke and myocardial infarction. The incidence of these serious side effects were 2.4 to 8.8% in the ranibizumab group compared to 4.9 to 5.5% in the sham group in the RISE/RIDE studies.

Given the rarity of these events, this study will not be powered to discern significant differences between the two comparison groups in the incidence in severe adverse events. As in any study, conclusions regarding the incidence of rare adverse events will not be able to be definitively determined in this study.

All adverse events will be reported to by the investigator and/or designee to the principal investigator and to the IRB.

### **3.5 COMPLIANCE WITH LAWS AND REGULATIONS**

This study will be conducted in accordance with current U.S. Food and Drug Administration (FDA) Good Clinical Practices (GCPs), and local ethical and legal requirements.

## **4. MATERIALS AND METHODS**

### **4.1 SUBJECTS**

#### **4.1.1 Subject Selection**

**30** subjects from approximately **1** site in the United States will be enrolled. Subjects will be recruited through clinics at the Cole Eye Institute, Cleveland OH. Eligible subjects will be administered and provided with a copy of informed consent. (See Appendix A, the study flow chart, for screening assessments). Fellow eyes that develop DME during the study period or have DME at study entry will be treated with ranibizumab at investigator discretion. Genentech will supply drug for the nonstudy eye. In the event that both eyes are eligible at study entry, the eye with more significant macular edema as defined by the central foveal thickness will be the study eye.

#### **4.1.2 Inclusion Criteria**

Subjects will be eligible if the following criteria are met:

- Ability to provide written informed consent and comply with study assessments for the full duration of the study
- Age  $\geq$  **18** years
- ETDRS best-corrected visual acuity of 20/25 to 20/320 in the study eye
- Willing, committed, and able to return for ALL clinic visits and complete all study related procedures
- At least 6 previous bevacizumab injections for diabetic macular edema in the last 12 months.
- At least 2 bevacizumab injections within 10 weeks and the most recent bevacizumab injection within 6 weeks of baseline study visits
- Persistent foveal-involving diabetic macular edema based on presence of intraretinal and/or subretinal fluid by SDOCT in the foveal center at study entry

#### **4.1.3 Exclusion Criteria**

Subjects who meet any of the following criteria will be excluded from this study:

- Pregnancy (positive pregnancy test) or lactation
- Premenopausal women not using adequate contraception. The following are considered effective means of contraception: surgical sterilization or use of oral contraceptives, barrier contraception with either a condom or diaphragm in conjunction with spermicidal gel, an IUD, or contraceptive hormone implant or patch.

- Intravitreal steroid or periocular steroid treatment within 3 months of study entry
- Focal/grid laser photocoagulation treatment within 3 months of study entry
- Panretinal photocoagulation treatment within 3 months of study entry
- Prior vitrectomy in the study eye
- History of retinal detachment in the study eye
- Prior trabeculectomy or other filtration surgery in the study eye
- Active intraocular inflammation in either eye
- Active ocular or periocular infection in either eye
- Active scleritis or episcleritis in either eye
- History of any other retinal vascular disease (e.g., retinal vein occlusion, retinal artery occlusion)
- Coexistent retinal disease other than diabetic retinopathy (e.g., AMD, inherited retinal disease)
- Intraocular surgery within 3 months of study entry.
- History of corneal transplant or corneal dystrophy
- Significant media opacities in study eye which may interfere with visual acuity
- Participation as a subject in any clinical study within 3 months of study entry.
- History of allergy to topical iodine
- Any other condition that the investigator believes would pose a significant hazard to the subject if the investigational therapy were initiated
- Participation in another simultaneous medical investigation or trial

## 4.2 METHOD OF TREATMENT ASSIGNMENT

Randomization to the two treatment groups will be utilized. The study is not masked.

## 4.3 STUDY TREATMENT

### 4.3.1 Formulation

Ranibizumab is formulated as a sterile solution aseptically filled in a sterile, 3-mL stoppered glass vial. Each single-use vial is designed to deliver 0.05 mL of 6 mg/mL ranibizumab aqueous solution with 10 mM histidine HCl, 10%,  $\alpha$ -trehalose dihydrate, and 0.01% polysorbate 20, pH 5.5. The results in the delivery of a 0.3 mg dose of ranibizumab. Each vial contains no preservative and is suitable for **single use only**.

Further details and molecule characterization will be included in the Investigator Brochure.

### 4.3.2 Dosage, Administration, and Storage

#### a. Dosage

Subjects will be randomized to two equal size treatment groups. The first group will be treated with 0.3 mg ranibizumab monthly for the duration of the study. The second group will be treated with 0.3 mg monthly for the first three months and will subsequently be treated with 0.3 mg on a “treat-and-extend” protocol (as outlined in 4.3.2b).

#### b. Administration

Group 1 will undergo monthly intravitreal injections of 0.3 mg ranibizumab administered **30 days (+/- 7 days)** following the last treatment for **12** months. Injections will be performed with sterile technique as outlined in appendix B.

Group 2 will be assigned to a “treat-and-extend” protocol. Eyes will be treated with 3 loading doses at 30-day (+/- 7 days) intervals. After the third loading dose, the follow-up interval is determined with an OCT-based protocol:

- **Criterion A:** If the central subfield thickness is less than or equal to 300 microns or there is complete absence of intraretinal or

subretinal fluid on the macular cube, the follow-up interval is increased by 2 weeks (+/- 7 days) at each visit [to a maximum interval of 12 weeks (+/- 7 days)]. The eye receives an intravitreal ranibizumab injection at every visit.

- **Criterion B:** If on subsequent follow-up visits, the thickness increases above 300 microns or there is recurrence of fluid with thickness above 300 microns, the interval is reduced by 2 weeks (+/- 7 days) (to a minimum interval of 4 weeks). Designated visits will also occur at 6 months and 12 months for visual acuity, ocular examination, FA, and OCT. No treatment will occur at these visits unless the time coincides with the scheduled “treat-and-extend” visit.
- **Criterion C: Rescue criteria** – If on subsequent follow-up visits, a patient loses > 15 letters with associated recurrence of fluid or central subfield thickness above 300 microns, the dosing interval will be immediately reduced to 4 weeks (+/- 7 days) for the next follow-up visit and for the residual duration of the study.
- **Criterion D:** Intervals following recurrence of fluid. If criterion B is met at any time, the patient will be reduced to a dosing interval as dictated above that maintains a central subfield thickness less than or equal to 300 microns or a complete absence of intraretinal or subretinal fluid on the macular cube. Once criterion A is met the dosing interval is again extended as outlined. If during a second extension period, criterion B is met, the patient is maintained at the dosing interval (less than where the second recurrence occurred) that maintains a central subfield thickness less than or equal to 300 microns or a complete absence of intraretinal or subretinal fluid on the macular cube for the rest of the study without further extension attempts.

All treatments will be administered at Cole Eye Institute at the Cleveland Clinic.

*\*See Appendix B for detailed pre-injection procedures.*

### **c. Storage**

Upon receipt, study drug kits should be refrigerated at 2°C - 8°C (36°F - 46°F). DO NOT FREEZE. Do not use beyond the expiration date. Ranibizumab vials should remain refrigerated. Protect vials from direct light. Store in original carton until time of use.

**RANIBIZUMAB VIALS ARE FOR SINGLE USE ONLY.** Vials used for one subject may not be used for any other subject.

## **4.4 CONCOMITANT AND EXCLUDED THERAPIES**

During the study period, no additional intravitreal or periocular pharmacologics can be administered, including but not limited to bevacizumab, aflibercept, and steroids. Focal laser photocoagulation is also not permitted during the study period. Panretinal photocoagulation is allowed if an eye develops retinal neovascularization, optic disc neovascularization, anterior segment neovascularization, and/or vitreous hemorrhage thought to be related to neovascularization.

Subjects may continue to receive all medications and standard treatments administered for their conditions at the discretion of their treating physician.

## **4.5 STUDY ASSESSMENTS**

### **4.5.1 Assessments during the Treatment Period**

#### **Screening/Day (-10 Days to Day 0)**

After the patient/subject has provided informed consent, the following information will be collected:

- Inclusion/exclusion
- Informed consent documentation
- Demographics
- Medical history and concurrent illnesses
- Concomitant medications

The following procedures and assessments will be conducted:

- ETDRS visual acuity with manifest refraction
- Slit lamp examination

- Fundus examination
- Spectral Domain OCT evaluation
- Ultra-widefield fluorescein angiogram
- Pulse and blood pressure
- Weight

### **Treatment Period**

#### **Baseline/Day 0/Month 0 (may occur at same time as screening visit)**

The following information will be collected:

- Inclusion/exclusion
- Informed consent documentation
- Demographics
- Medical history and concurrent illnesses
- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- ETDRS visual acuity with manifest refraction
- Slit lamp examination
- Fundus examination
- Spectral Domain OCT evaluation
- Intravitreal injection of ranibizumab
- Pulse and blood pressure

#### **Group 1 (Monthly treatment group): Month 1-Month 11 (+/- 7 Days)**

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- ETDRS visual acuity with manifest refraction
- Slit lamp examination
- Fundus examination
- Spectral Domain OCT evaluation

- Intravitreal injection of ranibizumab
- Ultra-widefield fluorescein angiogram (months 3 and 6)
- Pulse and blood pressure

**Group 1 (Monthly treatment group): End of Treatment/Month 12 (+/- 7 Days)/Early Termination visit**

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- ETDRS visual acuity with manifest refraction
- Slit lamp examination
- Fundus examination
- Spectral Domain OCT evaluation
- Ultra-widefield fluorescein angiogram
- Pulse and blood pressure
- Weight

**Group 2 (Treat-and-extend group): Month 1-Month 2 (+/- 7 Days)**

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- ETDRS visual acuity with manifest refraction
- Slit lamp examination
- Fundus examination
- Spectral Domain OCT evaluation
- Intravitreal injection of ranibizumab
- Pulse and blood pressure

**Group 2 (Treat-and-extend group): Month 3-Month 11 Follow-up Interval Based on OCT criteria as outlined sections 3.1 and 4.3.2b**

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- ETDRS visual acuity with manifest refraction
- Slit lamp examination
- Fundus examination
- Spectral Domain OCT evaluation
- Intravitreal injection of ranibizumab
- Ultra-widefield fluorescein angiogram [month 3 and 1<sup>st</sup> visit after week 22 of study entry (~ 6 month visit)]
- Pulse and blood pressure

**Group 2 (Treat-and-extend treatment group): End of Treatment/Month 12 (+/- 7 Days)/Early Termination visit**

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- ETDRS visual acuity with manifest refraction
- Slit lamp examination
- Fundus examination
- Spectral Domain OCT evaluation
- Ultra-widefield fluorescein angiogram
- Pulse and blood pressure
- Weight

### **Unscheduled visit**

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- ETDRS visual acuity with manifest refraction
- Slit lamp examination
- Fundus examination
- Spectral Domain OCT evaluation
- Intravitreal injection of ranibizumab (optional based on investigators discretion if greater than 4 weeks since last injection)
- Pulse and blood pressure

#### **4.5.2 Early Termination Assessments**

Subjects who withdraw from the study prior to completion should return for an early termination evaluation **30** days ( $\pm 7$  days) following the last injection/study visit for monitoring of all adverse events (serious and nonserious). The schedule of assessments for early termination is the same as that for the final visit.

#### **4.6 SUBJECT DISCONTINUATION**

Subjects have a right to withdraw from the study at any time.

The subject may be withdrawn from the study for any reasons: if it is in the best interest of the subject, intercurrent illness, adverse events, or worsening condition. The Cole Eye Institute/Cleveland Clinic or Justis P. Ehlers, MD (Principal Investigator) may request the withdrawal of a subject because of protocol violations, administrative reasons, or any other valid and ethical reasons.

If a subject discontinues from the study, he or she will not be allowed to re-enter the study.

Reasons for subject discontinuation may include, but are not limited to, the following:

- Sensory rhegmatogenous retinal detachment or Stage 3 or 4 macular hole
- Investigator determination that it is not in the best interest of the subject to continue participation
- Pregnancy
- Need for anti-VEGF therapy other than ranibizumab in the study eye, unless as a part of the prospective investigational study design
- SAE
- Any other safety concerns

In the event of an adverse event in the study eye that is considered by the investigator to be severe in intensity, serious consideration should be given to discontinuing the subject from the study.

#### **4.7 STUDY DISCONTINUATION**

This study may be terminated by Cole Eye Institute/Cleveland Clinic or Genentech at any time. Reasons for terminating the study may include the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Data recording is inaccurate or incomplete

#### **4.8 STATISTICAL METHODS**

##### **4.8.1 Analysis of the Conduct of the Study**

There is no formal sample size calculation in a pilot study. As this is a pilot study, a sample size of **30** patients is chosen, making sure that it is feasible to conduct the study and logistically to complete the study within **2** years.

If and when the study is planned for a phase II/III randomized control trial, appropriate statistical analysis will be determined.

#### **4.8.2 Safety Analyses**

Any adverse events, laboratory assessments, physical examinations, vital signs, ocular examinations and measurements from all **30** subjects will be utilized to summarize safety data for this pilot study.

##### **a. Primary Endpoint**

- Incidence and severity of ocular adverse events, as identified by eye examination (including visual acuity testing)
- Incidence and severity of other non-ocular adverse events, as identified by physical examination, subject reporting, and changes in vital signs

#### **4.8.3 Efficacy Analyses**

##### **a. Secondary Endpoints**

- Mean change from baseline in best-corrected visual acuity by the number of letters read correctly at months 6 and 12.
- Mean absolute change from baseline central foveal thickness at months 6 and 12 as measured by SDOCT (defined as the average thickness within the central 1 mm subfield)
- Proportion of eyes that were anatomically “dry” by SDOCT at months 6 and 12.
- Proportion of eyes gaining greater than or equal to 15 letters of vision at months 6 and 12.
- Proportion of eyes losing greater than or equal to 15 letters of vision at months 6 and 12.
- Proportion eyes with 20/40 or better best-corrected visual acuity at months 6 and 12.
- Comparison of angiography leakage from baseline to months 3, 6, and 12.
- Comparison of peripheral nonperfusion from baseline to months 3, 6, and 12.
- Comparison of previous anatomic anti-VEGF response to month 3, month 6, and month 12 anatomic response.
- Comparison of previous functional anti-VEGF response to month 3, month 6 and month 12 functional response

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#### **4.8.4 Missing Data**

Analyses of efficacy and safety will be based on available cases, without imputation for missing values.

#### **4.8.5 Interim Analyses**

An interim analysis is planned at 6 months. Reports of adverse events from this study may be reviewed and summarized periodically while the study is ongoing to ensure the safety of subjects.

#### **4.9 DATA QUALITY ASSURANCE**

Accurate, consistent, and reliable data will be ensured through the use of standard practices and procedures.

### **5. ASSESSMENT OF SAFETY**

#### **Specification of Safety Variables**

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to ranibizumab, all events of death, and any study specific issue of concern.

#### **5.1 ADVERSE EVENTS**

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with DME that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as intravitreal injections).

If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.

Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

## **5.2 SERIOUS ADVERSE EVENTS**

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

## **5.3 METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES**

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

### **Adverse Event Reporting Period**

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier.

### **Assessment of Adverse Events**

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to ranibizumab (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

### **Yes**

There is a plausible temporal relationship between the onset of the AE and administration of ranibizumab, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to ranibizumab; and/or the AE abates or resolves upon discontinuation of the ranibizumab or dose reduction and, if applicable, reappears upon re-challenge.

### **No**

Evidence exists that the AE has an etiology other than from ranibizumab (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to ranibizumab administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure.

Unexpected adverse events are those not listed in the Package Insert (P.I.) or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

## **5.4 EVALUATIONS**

Reviews of body systems will be performed.

Ophthalmologic evaluations will include slitlamp examination, dilated binocular indirect high-magnification ophthalmoscopy, measurements of BCVA and intraocular pressure. Diagnostic procedures will include SDOCT and ultra-

widefield fluorescein angiography if at appropriate visit (See Section 4.5 for a detailed description of the study assessments.)

## **5.5 VITAL SIGNS**

Pulse and blood pressure will be measured at protocol-specified study visits (see Section 4.5).

## **5.6 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS**

### **5.6.1 Eliciting Adverse Events**

A consistent methodology for eliciting AEs at all subject evaluation timepoints should be adopted. Examples of non-directive questions include:

- “How have you felt since your last clinical visit?”
- “Have you had any new or changed health problems since you were last here?”

### **5.6.2 Specific Instructions for Recording Adverse Events**

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

#### **a. Diagnosis vs. Signs and Symptoms**

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterix, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

**b. Deaths**

All deaths that occur during the protocol-specified AE reporting period (see Section 5.1.2), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

**c. Preexisting Medical Conditions**

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

**d. Hospitalizations for Medical or Surgical Procedures**

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

**e. Pregnancy**

If a female subject becomes pregnant while receiving investigational therapy or within 60 days after the last dose of study drug, a report should be completed and

expeditiously submitted to the Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the ranibizumab should be reported as an SAE.

**f. Post-Study Adverse Events**

If the investigator should become aware of an SAE occurring after a subject has completed or discontinued study participating if attributed to ranibizumab exposure, including, the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

**g. Reconciliation**

The Sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange monthly line listings of cases received by the other party. If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

**h. AEs of Special Interest (AESIs)**

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the Product.

The ranibizumab Events of Special Interest are:

- Endophthalmitis
- Intraocular inflammation (including vitritis and uveitis)
- Cataract (Traumatic)
- Increased IOP
- ATEs including stroke
- Retinal Pigment Epithelium Tear
- Retinal Detachment

**i. SAE Reporting**

Investigators must report all SAEs to Genentech within the timelines described below. The completed Medwatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:

**(650) 225-4682**  
**OR**  
**(650) 225-5288**

- Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.
- Serious AE reports that are related to ranibizumab and AEs of Special Interest (regardless of causality) will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date.
- Serious AE reports that are unrelated to the ranibizumab will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.

Additional Reporting Requirements to Genentech include the following:

- Any reports of pregnancy following the start of administration with the ranibizumab will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.
- All Non-serious Adverse Events originating from the Study will be forwarded in a quarterly report to Genentech.

### **5.6.3 MedWatch 3500A Reporting Guidelines**

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event

Description (section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

### **5.6.4 Follow-up Information**

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number,

if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at <http://www.fda.gov/medwatch/getforms.html>

### **5.6.5 Additional Reporting Requirements for IND Holders**

For Investigator-Sponsored IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

#### **7 Calendar Day Telephone or Fax Report:**

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of ranibizumab. An unexpected adverse event is one that is not already described in the ranibizumab Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

#### **15 Calendar Day Written Report**

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of ranibizumab. An unexpected adverse event is one that is not already described in the ranibizumab investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a Medwatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

**FDA fax number for IND Safety Reports:**

Fax: 1 (800) FDA 0178

**All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety:**

Fax: (650) 225-4682 or (650) 225-5288

**And to the Site IRB:**

Cleveland Clinic IRB  
9500 Euclid Ave  
Cleveland, OH 44195  
Phone 216.444.2924

**For questions related to safety reporting, please contact Genentech Drug Safety:**

Tel: (888) 835-2555

Fax: (650) 225-4682 or (650) 225-5288

## **IND Annual Reports**

### **Copies to Genentech:**

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-5288

### Study Close-Out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned contact for the study:

**5.6.6 SAFETY REPORTING FAX COVER SHEET**

**Genentech Supported Research**

AE / SAE FAX No: (650) 225-4682

Alternate Fax No: (650) 225-5288

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials  (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]
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SAE or Safety Reporting questions, contact Genentech Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

## **6.0 INVESTIGATOR REQUIREMENTS**

### **6.1 STUDY INITIATION**

Before the start of this study, the following documents must be on file with Cole Eye Institute/Cleveland Clinic or its appointed representative:

- FDA correspondence letter assigning an IND number or an IND waiver letter
- Original U.S. FDA Form 1571 (if applicable)
- Original U.S. FDA Form 1572 (for all studies conducted under U.S. Investigational New Drug [IND] regulations), signed by the Principal Investigator (if applicable)
- The names of any sub-investigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations.
- Current curricula vitae of the Principal Investigator
- Medical License
- Written documentation of IRB approval of the protocol (identified by Cole Eye Institute/Cleveland Clinic, protocol number or title and date of approval)
- IRB Approved protocol
- Fully executed contract
- Documentation of registration into clinical research website (e.g., [www.clinicaltrials.gov](http://www.clinicaltrials.gov)) (as applicable)
- Investigator Brochure Signature Receipt

### **6.2 STUDY COMPLETION**

The following data and materials are required by Cole Eye Institute/Cleveland Clinic before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period (if applicable)

- Case Report Forms properly completed by appropriate study personnel and signed and dated by the investigator (if applicable)
- Copies of protocol amendments and IRB approval/notification (if applicable)
- A summary of the study prepared by the Principal Investigator (will accept IRB summary close letter) (if applicable)
- All regulatory documents (e.g., curricula vitae for each Principal Investigator, U.S. FDA Form 1571 and 1572)

### **6.3 INFORMED CONSENT**

Informed consent documents will be provided to each subject.

The informed consent document must be signed and dated by the subject or the subject's legally authorized representative before his or her participation in the study. The case history for each subject shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The following basic elements must be included:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the patient's participation, a description of the procedures to be followed, and identification of any procedures or drug used for purposes which are experimental
- A description of any reasonably foreseeable risks or discomforts to the patients
- A description of any benefits to the patient or to others which may reasonably be expected from the research. A description that there may be no benefit from this research.

- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient
- A statement describing the extent, if any, to which confidentiality records identifying the patient will be maintained and that notes the possibility that the FDA and the Cole Eye Institute/Cleveland Clinic and the drug manufacturer may inspect the records
- For research involving more than minimal risk, an explanation as to whether any compensation and any medical treatments are available should injury occur and, if so, what they consist of or where further information may be obtained
- An explanation of whom to contact for answers to pertinent questions about the research and research patient's rights, and whom to contact in the event of a research-related injury to the patient
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled

#### **6.4 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE APPROVAL**

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB/EC for review and must be approved before the study is initiated. The study will be conducted in accordance with U.S. FDA, applicable national and local health authorities, and IRB/EC requirements.

The Principal Investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case the IRB/EC must be updated at least once a year. The Principal Investigator must also keep the IRB/EC informed of any significant adverse events.

Investigators are required to promptly notify their respective IRB/EC of all adverse drug reactions that are both serious and unexpected. This generally

refers to serious adverse events that are not already identified in the Investigator Brochure and that are considered possibly or probably related to the study drug by the investigator. Some IRBs or ECs may have other specific adverse event requirements that investigators are expected to adhere to. Investigators must immediately forward to their IRB/EC any written safety report or update provided by Cole Eye Institute/Cleveland CLinic (e.g., IND safety report, Investigator Brochure, safety amendments and updates, etc.).

## **6.5 CASE REPORT FORMS**

All CRFs should be filled out completely by appropriate personnel. The CRF should be reviewed, signed, and dated by the investigator.

All CRFs should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced CRF copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. **DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID ON THE ORIGINAL.**

## **6.6 STUDY DRUG ACCOUNTABILITY**

The Investigator is responsible for the control and distribution of study drug.

All partially used or empty containers should be disposed of at the study site according to institutional standard operating procedure.

## **6.7 DISCLOSURE OF DATA**

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA, national and local health authorities, the drug manufacturer and the IRB/EC for each study site, if appropriate.

## **6.8 RETENTION OF RECORDS**

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after the investigation is discontinued and the U.S. FDA and the applicable national and local health authorities are notified.

## **6.9 STUDY CLOSE-OUT**

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be faxed to the assigned Clinical Operations contact for the study:

Lucentis IST Program Fax: 1-866-551-1893

:

## REFERENCES:

1. Wessel MM, Nair N, Aaker GD, Ehrlich JR, D'Amico DJ, Kiss S. Peripheral retinal ischaemia, as evaluated by ultra-widefield fluorescein angiography, is associated with diabetic macular oedema. *The British journal of ophthalmology* 2012;96:694-8.
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## APPENDIX A

### Study Flowchart

#### Group 1: Monthly Treatment Group

	Pretreatment	Assessments During Treatment (Months)—visit 30 days (+/- 7 days) after last treatment											Follow-Up Assessments		
	Screen*	0*	1	2	3	4	5	6	7	8	9	10	11	End of Study Month 12	Unscheduled Visit
Informed consent	X	X													
Demographic data	X	X													
Medical history	X	X													
Vital signs (pulse/BP)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X													X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Slit Lamp Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ETDRS Manifest Refraction/Complete eye exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SDOCT both eyes	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Intravitreal Ranibizumab Injection		X	X	X	X	X	X	X	X	X	X	X	X		X**
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fluorescein Angiography	X				X			X						X	

\* Screening and visit at month zero may occur on the same day. \*\* If treatment criteria met as outlined and at least 4 weeks has passed since the last injection.

**Group 2: Treat and Extend Group**

	Pretreatment	Assessments During Treatment (Months) — visit 30 days (+/- 7 days) after last treatment				Follow-Up Assessments	
	Screen*	0*	1	2	Month 3-11, timing per T & E protocol	End of Study Month 12	Unscheduled Follow-up Visit
Informed consent	X	X					
Demographic data	X	X					
Medical history	X	X					
Vital signs (pulse/BP)	X	X	X	X	X	X	X
Weight	X					X	
Concomitant Medication	X	X	X	X	X	X	X
Slit Lamp Exam	X	X	X	X	X	X	X
Fundus Examination	X	X	X	X	X	X	X
ETDRS Manifest Refraction/Complete eye exam	X	X	X	X	X	X	X
SDOCT both eyes	X	X	X	X	X	X	X
Intravitreal Ranibizumab Injection		X	X	X	X		X***
AE monitoring	X	X	X	X	X	X	X
Fluorescein Angiography	X				[X]**	X	

\* Screening and visit at month zero may occur on the same day. \*\* Angiography to be performed at month 3 visit and at the first visit after week 22 (~ 6 month visit). \*\*\* If treatment criteria met as outlined for group 2 and at least 4 weeks have passed since last injection. T & E: Treat and Extend



## **APPENDIX B**

### **Pre-Injection Procedures for All Subjects**

In order to minimize the risk of potential adverse events associated with serial intravitreal injections (e.g., endophthalmitis), aseptic technique will be observed by clinic staff involved in the injection tray assembly, anesthetic preparation, and study drug preparation and administration. Intravitreal injection procedures will be performed in accordance with standard injection procedures at the Cleveland Clinic.

The intravitreal injection procedure will be carried out under controlled aseptic conditions, which include the use of sterile gloves, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide (e.g., betadine) should be given prior to the injection.

## APPENDIX C

### Analysis of Similar Events Template for IND Safety Reports

#### IND Safety Report

##### Case Summary

*This section will be initiated by a research coordinator and may be modified by principal investigators if necessary. The case summary should describe the reported AE in detail, including a description of what happened and a summary of all relevant clinical information (e.g. medical status prior to the event, signs, symptoms, diagnoses, clinical course, treatment, outcome, etc.) The IND safety report should not identify the subject ID #, reporting investigator, or the site as this information may compromise the study blind.*

##### PREVIOUS REPORTS

*The information for this section comes from Principal Investigator and the search of similar events. This section should be written by the responsible principal investigator.*

*\* Select one of the following two statements after reviewing the search of similar events results.*

Under IND \_\_\_\_\_ (insert IND#), the following IND safety reports of similar AEs have been previously submitted:

MCN	Reported Event	Submission Date

Or

Under IND \_\_\_\_\_ (insert IND#), no IND safety reports of similar AEs have been submitted previously.

*In addition to previously submitted IND safety reports of similar events, this section can also summarize previous serious reports of the same/similar event that were considered unrelated to the investigational product at the time of the reporting. These events would remain blinded, unless a decision to unblind is made by an Independent Monitoring Committee for reasons of subject protection. The decision on what similar events to summarize in this section should be made after reviewing the similar events report generated by Clinical Data Management. If a safety signal is particularly worrisome (e.g., a study stopping type of event), a more extensive evaluation may be required.*

##### Assessment of Relationship

*After evaluation the new case report and reviewing any relevant previous reports of similar events, the PI selects one of the following boilerplate conclusion statements, if applicable. The PI may also craft an alternative conclusion.*

Based on review of available data, **Cleveland Clinic** believes there is a reasonable possibility of a cause-and-effect relationship between administration of \_\_\_\_\_ (insert study drug name) and the occurrence of \_\_\_\_\_ (insert AE).

*Additional information on risk factors and/or treatment of the AE may be provided if warranted.*

Or

Based on review of available data, the **Cleveland Clinic** does not believe that there is a reasonable possibility of a cause-and-effect relationship between administration of \_\_\_\_\_(insert study drug name) and the occurrence of \_\_\_\_\_(insert AE).

*Explain if warranted. Do not speculate.*

Or

Based on review of available data, the **Cleveland Clinic** cannot establish or exclude the possibility of a cause-and-effect relationship between administration of \_\_\_\_\_(insert study drug name) and the occurrence of \_\_\_\_\_(insert AE).

*Explain if warranted. Do not speculate.*

After review of the clinical details and investigator's comments pertaining to this AE, and based on experience to date, the **Cleveland Clinic** does not believe that changes to the conduct of this clinical trial are warranted. *This statement can be modified if changes to the conduct of the clinical trial are made.*

## Appendix D: Quantitative Assessment of Ultra-widefield Angiographic Features in Diabetic Macular Edema Addendum

Examples of quantitative segmentation of leakage and ischemia in ultra-widefield angiography. Quality permitting, UWFA obtained during study will be assessed for quantitative changes.

Figure 1: Diabetic macular edema and proliferative diabetic retinopathy with automated identification of retinal vascular leakage (green). Longitudinal assessment following anti-VEGF treatment. Areas of segmentation (e.g., green) able to be quantified in absolute or relative fashions for area.

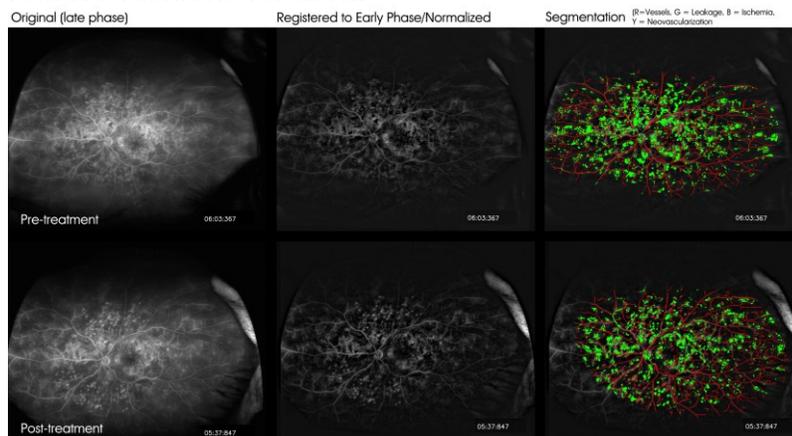
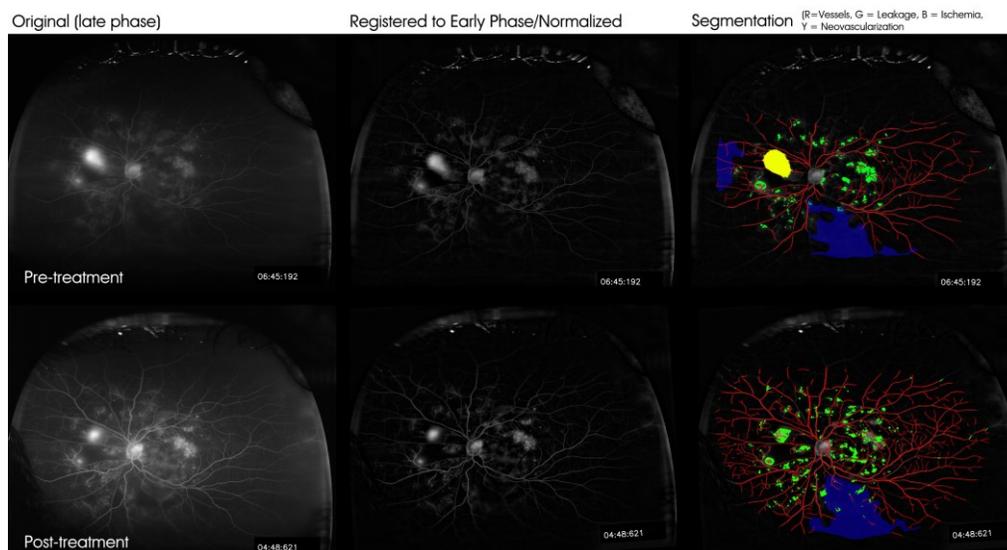


Figure 2: Diabetic macular edema and proliferative diabetic retinopathy with automated identification of neovascular leakage (yellow), ischemia (blue) and retinal vascular leakage (green). Longitudinal assessment following anti-VEGF treatment. Areas of segmentation (e.g., green, yellow, blue) able to be quantified in absolute or relative fashions for area.



## **Appendix E: Pre-Ranibizumab Assessment of Anti-VEGF Therapeutic Response.**

- As part of the screening process for REACT, the medical records are reviewed for prior treatment, medical history, and ophthalmic history information for assessment of inclusion and exclusion criteria. The same medical record will be reviewed for specific data on functional (visual acuity) and anatomic (OCT) data on response to bevacizumab prior to exposure to ranibizumab in the trial. This will be performed in a retrospective fashion without any additional contact with study subjects or study interventions. Overall response to therapy as well as stratification to ranibizumab response will be assessed (e.g., dramatic responder vs nonresponder). Subjects would also be evaluated in the context of their bevacizumab response (nonresponder vs incomplete responder vs tachyphylaxis).

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